REMARKS/ARGUMENTS

Claims 27-33 are currently pending. Claims 28, 31 and 32 are amended herein. No new matter has been added.

Claim 31 Rejected for Failure of Written Description

Claim 31 remains rejected for failure of written description. Applicants respectfully disagree. However, in the interest of expediting the prosecution of the application, Applicants hereby amend Claim 31 to recite "acetate ester." Reconsideration is sincerely solicited.

Claims 28, 32, and 33 Rejected for New Matter

Claims 28, 32 and 33 remain rejected for lack of written description of a bacterium cell having reduced activity of *ack* or *pta*. Applicants respectfully disagree. However, in the interest of expediting the prosecution of the application, Applicants hereby amend Claims 28 and 32 to recite "*ackA* and *pta*." Reconsideration is sincerely solicited.

Claim 31 Rejected for Failure of Enablement

Claim 31 remains rejected for the reason that the claim is not enabled for the use of alcohols. Applicants respectfully disagree. However, in the interest of expediting the prosecution of the application, Applicants hereby amend Claim 31 to delete the recitation of alcohol. Reconsideration is sincerely solicited.

Claims 27-33 Rejected as Obvious

Claims 27-33 remain rejected as being obvious in light of San, Song, Vallari, Voet, and Yang. Applicants respectfully disagree.

First, Applicants repeat all arguments presented to the Examiner on December 7, 2007 in response to a Non-Final Office Action issued to this application. The arguments are incorporated herein by reference in their entireties to avoid redundancy. Specifically, Applicants have argued that:

- Recombinant pdh Element Not Taught;
- Supplementation with Pantothenate Element Not Taught;
- Motivation to Combine Not Shown;
- Reasonable Expectation of Success Not Shown;
- Prima Facie case Not Made;
- Competent Evidence Required;
- Hindsight Impermissible;
- Unexpected Flux Increase; and
- Unexpected Supplementation Requirement.

In the current response, Applicants submit the following additional arguments to traverse the obviousness rejection on Claims 27-33. Reconsideration is sincerely solicited.

METABOLIC ENGINEERING NOT PREDICTABLE: In the instant Office Action, the Examiner has held that the current invention is predictable, the success is anticipated, and the claimed methods are of ordinary skill and common sense. Applicant respectfully disagrees.

Metabolism processes are complex. Multiple processes are often intersected and mingled together to form a network of routes and pathways. Manipulating one particular process often does not produce predictable result if interconnections exist. This phenomenon has been widely documented in scientific articles.

For example, in *Functional Ingredient Production: Application of Global Metabolic Models*, Smid, et al., Current Opinion in Biotechnology 16:190–197 (2005), p. 190, it is stated that:

> The phenotypic effects of engineering single metabolic pathways can **only be predicted accurately if the pathway is relatively isolated from the overall metabolism**. If for instance important cofactors or key metabolites such as nicotinamide adenine dinucleotide (NAD+), ATP, **acetyl-CoA** or folate are crucial for the pathway of interest, the impact of pathway

> engineering on the overall metabolism and, therefore, on product yields is complicated by the participation of these cofactors in many other pathways of the metabolic network.
>
> . . .
>
> The main challenge of engineering the biosynthesis pathways of cofactors or of other so-called currency metabolites is the **high degree of metabolic connectivity** of these compounds (i.e. the number of reactions in which the compounds participate).
>
> . . .
>
> Therefore, changes in cofactor pool sizes caused by metabolic engineering will lead, in many cases, to **unexpected** or even **counter-intuitive** phenotypes.

In *Pantothenate Kinase and Control of CoA Synthesis in Heart*, Robishaw et al., Am. J. Physiol., 246 (Heart Circ. Physiol. 15): H532-H541 (1984), p. H538, the author also observed that:

> When control of a metabolic pathway in intact tissue is studied, every step in the pathway must be considered as a potential site of control. Many of the enzymes in a pathway may be subject to regulation by external factors when studied **in isolation** but do **not** regulate flux through the pathway in **the cell**.

Therefore, Applicant respectfully submits that the current invention is not predictable based on each individual pathway's performance **in isolation**. Reconsideration is sincerely solicited.

CONCLUSIONS

Each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue. Therefore, Applicants request allowance of at least these claims. Applicants respectfully request the Examiner contact them if there are any questions or issues that need to be addressed.

No fees are believed to be due for this submission. However, the Commissioner is hereby authorized to charge any required fees, or credit any overpayment, to Deposit Account No. 50-3420 (reference 31175413-005002 M. Dai)

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Respectfully submitted,

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